REMARKS

Claims 33-64 are pending in the above-identified patent application. Reexamination and reconsideration of the application are requested in view of the following remarks.

Claim Rejections under 35 U.S.C. §112, first paragraph.

The Examiner rejects Claims 33-64 under 35 U.S.C. §112, first paragraph, for lack of enablement. Applicants respectfully traverse the rejection.

The Examiner indicates that the specification is enabling for a method of inhibiting melanoma cell growth comprising direct administration to melanoma cells of mycobacterial compositions (MCC, *M. phlei* DNA, BCC, or B-DNA) and a chemotherapeutic agent, wherein the composition and the chemotherapeutic agent display an anti-cancer synergism. The Examiner asserts that the specification of the present application does not provide enablement for methods of treating any type of cancer by administering a combination of a mycobacterial composition (MCC, *M. phlei* DNA, BCC, or B-DNA) and a chemotherapeutic agent, wherein the combination treatment is administered by any means other than direct administration.

Applicants respectfully disagree. As noted by the Examiner, factors to be considered in determining whether a disclosure meets the enablement requirement of 35 U.S.C. §112, first paragraph, have been described in *In re Wands*, 8 USPQ2d1400 (CA FC 1988), which states on page 1404:

> "Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman. They include (1) the quantity of the experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

The state of the prior art and unpredictability of the art

The Examiner asserts that "the prior art indicates that there are a number of problems related to pharmaceutical administration of mycobacterial DNA/cell wall compositions for the treatment of cancer." In support of his position, the Examiner cites *Morales*, 1995 (*J. Urol.* 153:1706-1710). Applicants respectfully bring to the Examiner's attention that the methods of the present invention differ from the methods taught in *Morales*. *Morales* teaches administration of *M. phlei* cell wall (MCW) for treatment of prostate tumors. In contrast, the methods as claimed in the present application comprise administration of mycobacterial compositions (MCC, *M. phlei* DNA, BCC, or B-DNA) in combination with a chemotherapeutic agent. Therefore, the teachings of *Morales* cannot be applied to the methods of the present invention.

Working examples and guidance provided

The Examiner asserts that "[t]he working examples presented in the specification only indicate the treatment of melanoma cells by directly administering the compounds to melanoma cells in vitro", and that "there is no indication in the specification that any type of cancer cell other than melanoma cells were responsive the combination of drugs" [sic].

Applicants respectfully bring to the Examiner's attention that the specification provides a teaching of treatment of various types of cancer cells with the claimed compositions, in addition to melanoma cells. For example, the data disclosed in Example 6 (page 10, line 33, through page 11, line 12) demonstrate that MCC induces cell cycle arrest in methothrexate-treated Jurkat (human leukemia), HL-60 (human promyelocytic leukemia), HL-60MX1 (human promyelocytic leukemia), EL-4 (murine lymphoma), and B-16 (melanoma) cancer cells.

Applicants also submit herewith the Declaration of Dr. Mario C. Filion under 37 C.F.R. §1.132. The Declaration provides additional data regarding the effectiveness of mycobacterial compositions in combination with various chemotherapeutic drugs for

inhibition of proliferation of Jurkat T cell leukemia, EL-4 T-cell lymphoma, and LNCaP prostate cancer cells.

In view of the foregoing, Applicants respectfully assert that the specification and Declaration provide several working examples regarding the treatment of various types of cancer by mycobacterial compositions in combination with chemotherapeutic drugs.

The Examiner asserts that, "although the combination treatments disclosed have been shown to have synergistic effect on inhibiting melanoma cell division in vitro, there is no indication that the treatments would have an identical synergistic effect on inhibiting melanoma cell division (or any other type of cancer cell) in vivo." Applicants respectfully assert that the *in vitro* cancer models used in the working examples would be recognized by one skilled in the art as correlating to treatment of cancer *in vivo*.

The Examiner states that, according to Figure 8, "there is no indication that MCC treatment results in any cytotoxic effect on cancer cells," and, "[t]herefore, there is no indication that the claimed combination treatments would result in killing of any cancer cell either in vitro or in vivo, a feature critical to treating cancer." Figure 8 shows the results of the cytotoxicity assay measuring the release of lactate dehydroenase (LDH) resulting from the loss of membrane integrity (see Example 14, page 17, lines 20-31). Example 14 teaches that, "[a]s shown in Fig.8, MCC itself was not cytotoxic to the B16 melanoma cells", which "demonstrates that MCC <...> does not act by disrupting the cell membrane." On the other hand, Examples 12 (page 16, lines 13-29) and 13 (page 17, lines 1-19) teach, respectively, that mycobacterial compositions of the present invention induce apoptosis in B-16 melanoma cells, and lead to a significant increase in the activity of interleukin-1-converting enzyme (ICE/caspase-1) involved in the activation of the caspase cascade leading to apoptosis. Therefore, Figure 8 does not demonstrate that the treatments of the present invention do not inhibit cell proliferation, but shows that the treatments do not result in the cell membrane disruption as measured by the applied assay. Therefore, Figure 8 does not indicate that the claimed treatments would not be effective for treating cancer.

The Examiner asserts that "there is not guidance in the specification indicating how to effectively administer the compounds to different kinds of tumors." Applicants respectfully bring to the Examiner's attention that the specification teaches (on page 8, line 37, through page 9, line 7), various routes of administration of the compositions of the present invention.

It is Applicants' position that the application provides sufficient guidance on effectively using the claimed methods. Applicants respectfully assert that, in view of the working examples provided in the specification and in the Declaration, the correlation between *in vitro* cancer models and *in vivo* cancers known to one of ordinary skill in the art, and high level of one of ordinary skill in art, recognized by the Examiner, that one skilled in the art would not require undue experimentation in order to effectively use the claimed methods of the present invention to treat cancer *in vivo* with a reasonable expectation of success.

In view of the foregoing, Applicants respectfully assert they have overcome the rejection under 35 U.S.C. §112, first paragraph, and request its withdrawal.

CONCLUSION

The foregoing is submitted as a full and complete response to the non-final Office Action mailed December 17, 2002. Applicants assert that the claims are now in condition for allowance and respectfully request that the application be passed to issuance. If the Examiner believes that any informalities remain in the case, which may be corrected by Examiner's amendment, or that there are any other issues which can be resolved by a telephone interview, a telephone call to the undersigned agent at (404) 815-6500 or to Dr. John K. McDonald at (404) 745-2470 is respectfully solicited.

No additional fees are believed due, however, the Commissioner is hereby authorized to charge any deficiencies which may be required or credit any overpayment to Deposit Account Number 11-0855.

Respectfully submitted,

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